REMARKS

I. Amendments

By this amendment, Claim 1 has been amended to incorporate specific limitations of the dependent claim 9. The amendment is made without prejudice to the filing of future continuing applications. New Claim 28 is directed to the specific subject matter of previously pending claim 1 and 13.

This amendment adds no new matter to the specification

No amendment of inventorship is necessitated by this amendment.

II. Traverse of the Rejection of Claims 1 and 9 under 35 U.S.C. Sec. 102(b) over Stevenson *et al.*

Claims 1 and 9 stand rejected. Claim 1 has been amended to incorporate the limitation of Claim 9, and independent Claim 28 newly added in place of now canceled Claim 13.

Applicants traverse the rejection, Claim 1 and new Claim 27 are not anticipated by the teaching of Stevenson *et al.* (The Diabetes Annual, 1995 article).

1) The Examiner has admitted that "the prior art does not expressly disclose the employment of the particular thiazolidinedione derivative, 5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, in a method for treating a Tumor Necrosis Factor-α mediated diabetic complications in a mammal, and its effective amount." (Paper 15, page 4, 3rd paragraph).

2) Claim 1 is limited to the administration of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (pioglitazone) for the treatment of Tumor Necrosis Factor-alpha (TNF-α) mediated diabetic complications.

The Examiner has improperly expanded the scope of Stevenson *et al.* to make the rejection. Anticipation requires that each and every limitation of the claimed invention be taught by a single art reference.

Stevenson *et al.* do not teach or demonstrate any data to support the treatment of TNF-α mediated diabetic complications with pioglitazone or rosiglitazone. Contrary to the Examiner's assertion, Stevenson et al. only describe data and hypothetical mechanisms regarding the administration of englitazone and ciglitazone and measurement of the reduction of Islet amyloid polypeptide, (IAPP, amylin). (Stevenson *et al.* pages 185-186).

The Examiner attempts to use an anecdotal reference to work reported by C. Hoffman *et al.* to support the rejection. The comment by Stevenson *et al.* (page 186) is made, without experimental evidence or data. The actual C. Hoffman *et al.*, Endocrinology Vol. 134 (1): pp. 264-270 reference was cited in an IDS and form PTO-1449 by Applicants as reference A9.

The comment by Stevenson *et al.* is mere conjecture at best, and does not attempt to assert a method of treatement. Hoffman *et al.* do not teach a method for treating TNF-α mediated complications of diabetes by the administration of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (pioglitazone).

The cited conjecture by Stevenson *et al.* should not be substituted for the actual teaching of the primary reference. Stevenson *et al.* even admits that the primary reference, in fact teaches that the described effect on TNF-α cannot be attributed to administration of pioglitazone alone. Thus, the statement cannot be construed as teaching a method for treating Tumor Necrosis Factor-alpha (TNF-α) mediated diabetic complications. The mere suggestion that TNF-α is associated with diabetes does not teach or suggest the specifically claimed method for treating TNF-α mediated diabetic complications with pioglitazone and/or rosiglitazone of the present invention.

A new method of treatment for a previously know chemical compound is not anticipated by the administration of the compound in a previously known method. In the invention of Claim 1 as amended, is specifically for the administration of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (pioglitazone) for the treatment of Tumor Necrosis Factor-alpha (TNF-α) mediated diabetic complications. This is distinct from the treatment of diabetes as was taught in the art.

This rejection should be withdrawn.

3) Claim 1 is limited to the administration of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (pioglitazone) for the treatment of

Tumor Necrosis Factor-alpha (TNF-α) mediated diabetic complications selected from the group of retinopathy, nephropathy, neuropathy and disorders of the arteries.

The mere suggestion that TNF-α is associated with diabetes does not teach the specifically claimed method for treating TNF-α mediated diabetic complications selected from the group of retinopathy, nephropathy, neuropathy and disorders of the arteries, with pioglitazone and/or rosiglitazone of the present invention.

The cited reference does not teach or suggest this limitation.

This rejection should be withdrawn.

4) Claim 1 is limited to the administration of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (pioglitazone) for the treatment of Tumor Necrosis Factor-alpha (TNF-α) mediated diabetic complications selected from the group of retinopathy, nephropathy, neuropathy and disorders of the arteries at a dose of 0.1 mg/kg to 30 mg/kg.

The cited reference only demonstrates data for englitazone and ciglitazone and measurement of the reduction of Islet amyloid polypeptide, (IAPP, amylin). (Stevenson *et al.* pages 185-186). This does not teach or anticipate the claimed invention.

This rejection should be withdrawn.

III. Traverse of the Rejection under 35 U.S.C. Sec. 103(a) over Stevenson *et al.* in view of Sohda *et al.*

Claim 13 was rejected as being unpatentable over Stevenson *et al.* (The Diabetes Annual, 1995 article) and Sohda *et al.* (WO 96/05186). As new Claim 28 incorporates the now cancelled Claim 13, this rejection is traversed.

Applicants respectfully request withdrawal of the Sec. 103(a) rejection over Stevenson *et al.* and Sohda *et al.* The general teaching that thiazolodines are useful for treating diabetes, does not teach or suggest the claimed invention.

The Examiner admits that none of the asserted art teach treatment of TNF-alpha mediated inflammation. (Paper 13, Page 7, 1st paragraph, and Page 9, 4th paragraph). There is no evidence

on record to support maintaining this rejection. The Examiner has admitted that "the prior art does not expressly disclose the employment of the particular thiazolidinedione derivative, 5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, in a method for treating a Tumor Necrosis Factor-α mediated diabetic complications in a mammal, and its effective amount." (Paper 15, page 4, 3rd paragraph).

The causes of diabetes, and the related pathologies are complex. It is improper to mistakenly over characterize the teaching of the art, and then to assert that the general teachings of treatment of diabetes can be used to suggest the specific claimed invention as obvious.

As stated in the MPEP in accordance with the Law:

Patent Examiners carry the responsibility of making sure that the standard of patentability enunciated by the Supreme Court and by the Congress is applied in each and every case. The Supreme Court in *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966), stated:

> Under §103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquires may have relevancy. . .
>
> This in not to say, however, that there will not be difficulties in applying the nonobviousness test. What is obvious is not a question upon which there is likely to be uniformity of thought in every given factual context. The difficulties, however, are comparable to those encountered daily by the courts in such frames of reference as negligence and scienter, and should be amenable to a case-by-case development. We believe that strict observance of the requirements laid down here will result in that uniformity and definitiveness which Congress called for in the 1952 Act.

Office policy has consistently been to follow *Graham v. John Deere Co.* in the consideration and determination of obviousness under 35 U.S.C. 103. As quoted above, the four factual inquires enunciated therein as a background for determining obviousness are briefly as follows:

(A) Determining of the scope and contents of the prior art;

(B) Ascertaining the differences between the prior art and the claims in issue;

(C) Resolving the level of ordinary skill in the pertinent art; and

(D) Evaluating evidence of secondary considerations.

The Supreme Court reaffirmed and relied upon the *Graham* three pronged test in its consideration and determination of obviousness in the fact situations presented in both the *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 189 USPQ 449, reh'g denied, 426 U.S. 955 (1976) and *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 163 USPQ 673 (1969) decisions. In each case, the Court went on to discuss whether the claimed combinations produced a "new or different function" and a "synergistic result," but clearly decided whether the claimed inventions were nonobviousness on the basis of the three-way test in *Graham*.

Accordingly, examiners should apply the test for patentability under 35 U.S.C. 103 set forth in *Graham*. It should be noted that the Supreme Court's application of the *Graham* test to the fact circumstances in *Ag Pro* was somewhat stringent, as it was in *Black Rock*. Note *Republic Industries, Inc. v. Schlage Lock Co.*, 592 F.2d 963, 200 USPQ 769 (7th Cir. 1979). The Court of Appeals for the Federal Circuit stated in *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1540, 218 USPQ 871, 880 (Fed. Cir. 1983) that a requirement for "synergism" or a "synergistic effect" is nowhere found in the statute, 35 U.S.C. When present, for example in a chemical case, synergism may point toward nonobviousness, but its absence has no place in evaluating the evidence on obviousness. The more objective findings suggested in *Graham*, supra, are drawn from the language of the statute and are fully adequate guides for evaluating the evidence relating to compliance with 35 U.S.C. §103. *Bowser Inc. v. United States*, 388 F. 2d 346, 156 USPQ 406 (Ct. Cl. 1967).

When applying 35 U.S.C. 103, the following tenets of patent law must be adhered to:

(A) The claimed invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention and

(D) Reasonable expectation of success is the standard with which obviousness is determined.

Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

(*See The MPEP v7r1 §2141*).

In making the present rejection under §103, the Examiner has failed to follow the proscribed Patent Office policy, and has failed to make any findings upon which the *Graham* factors can be applied to the claimed invention. As such, the Examiner's rejection clearly fails to make a *prima facie* case for a rejection under §103.

The Examiner's analysis is clearly faulty, and fails to consider the art as a whole in comparison to the claimed invention considered as a whole. It is admitted by the Examiner that there is no teaching in the cited art of the method of the specific claimed invention. The Examiner admits that none of the asserted art teach treatment of TNF-alpha mediated inflammation. (Paper 13, Page 7, 1st paragraph, and Page 9, 4th paragraph).

The Examiner's personal opinion cannot be substituted for the lack of motivation or suggestion in the cited art. There must be some suggestion or teaching in the cited art itself for making the asserted combination. *In re Geiger* 815 F.2d 686, 2 USPQ2d 1276 (CAFC 1987). Only the suggestion of the Examiner, using the teaching of the present invention as a guide, prompts the asserted combination of art. This is an improper use of hindsight to reconstruct the claimed invention from the art without proper motivation being found in the asserted art itself. The Examiner has failed to cite any motivation or teaching in the cited art to make the asserted combination of art, or which would support the asserted rejection. The teaching of the cited Stevenson et al. reference is silent as to the administration of the compound of the claimed invention method. The teaching of Sohda et al. fails to suggest the claimed treatment of Tumor Necrosis Factor-α mediated complications of diabetes. Thus, there is no teaching or suggestion in the cited art to combine such references to arrive at the claimed invention. Art which give only

general guidance and is not specific as to the particular form of the claimed invention and how to achieve it, cannot render claims obvious. *Ex parte Obukowicz* 27 USPQ2d 1063 (BPAI 1992).

The Examiner further asserts, without support in the asserted art or any cited art that "one of ordinary skill in the art at the time of the invention would have been motivated to optimize the effective amounts..." (Paper 15, page 5, last paragraph).

The Examiner's rejection amounts to no more than an invitation to experiment, as it is *not suggested or taught* in the asserted art what specific suitable amount would result in a useful and effective composition. *Ex parte Obukowicz* 27 USPQ2d 1063 (BPAI 1992). The Examiner's asserted motivation is clearly made in hindsight as the language used "to optimize the effective amounts" clearly relies upon the teaching of the present invention to suggest and teach *that there even would be* a desirable effective amount to optimize. Hindsight obviousness after the invention has been made is not the test. *In re Carroll* 601 F.2d 1184, 202 USPQ 571 (CCPA 1979).

The Examiner's assertion of routine experimentation is not based upon any cited art, and clearly illustrates an improper use of hindsight using the claimed invention as a guide for creating the perceived rejection. The Examiner asserts an improper standard for obviousness, since even routine experimentation may not establish obviousness absent a reasonable expectation of success, or a motivation in the cited art to make the modifications of the claimed invention. In the chemical arts, which are largely empirical, it is therefore highly difficult to predict with reasonable certainty how any given compound will behave. *In re Carleton* 599 F.2d 1021, 202 USPQ2d 165 (CCPA 1979). Because chemistry is often an empirical science, it is easy to characterize inventions in this field as the result of "routine testing". But even "routine testing" must be guided and directed by the mental concept of the inventor. "Routine testing" does not negate patentability. *In re Fay et al.* 347 F.2d 597, 146 USPQ 47 (CCPA 1965).

The cited Stevenson reference only demonstrates data for englitazone and ciglitazone and measurement of the reduction of Islet amyloid polypeptide, (IAPP, amylin). (Stevenson *et al.* pages 185-186). Compound (I) of the Sohda reference does not cover any form of pioglitazone or rosiglitazone, as both compounds lack the partial structure of Y that is a bivalent hydrocarbon as taught by the Sohda reference. Thus no asserted combination of the art teaches each and every limitation of the claimed invention.

Since the Examiner has failed to establish a *prima facie* case of obviousness, this rejection must be withdrawn.

IV. Double Patenting Rejection

Applicants respectfully traverse the Examiner's obviousness-type double patenting rejection of Claims 1, 9 and 13 over US Patent No. 5,965,584 in view of Stevenson *et al.* (The Diabetes Annual, 1995 article).

The Examiner's asserted reasoning for the rejection is improperly based upon an incorrect characterization of the cited art, and a misapplication of state of the art at the time of the invention. The Examiner's rejection improperly relies upon hindsight to validate the reasoning of the rejection.

US Patent 5,965,584 teaches the use of pioglitazone and its salts for treating diabetes in mammals. Cited claims 6 and 12 specifically recite a method for treating diabetes. The asserted claims 6 and 12 require the administration of a biguanide in combination with an insulin sensitivity enhancer. The treatment of diabetes of claims 6 and 12 do not teach or suggest treating Tumor Necrosis Factor-alpha mediated diabetic complications by the administration of pioglitazone alone.

The Examiner asserts that "Stevenson teaches that Tumor Necrosis Factor-α (TNF-α) is know to increase insulin insensitivity (see page 185), and is thus tightly associated with diabetic complications." (Page 7, 2nd to last paragraph).

Stevenson *et al.* do not teach or demonstrate any data to support the treatment of TNF-α mediated diabetic complications with pioglitazone or rosiglitazone. Contrary to the Examiner's assertion, Stevenson et al. only describe data and hypothetical mechanisms regarding the administration of englitazone and ciglitazone and measurement of the reduction of Islet amyloid polypeptide, (IAPP, amylin). (Stevenson *et al.* pages 185-186).

The Examiner, in a prior rejection, attempts to use an anecdotal reference to work reported by C. Hoffman *et al.* to support the rejection. The comment by Stevenson *et al.* (page 186) is made, without experimental evidence or data. The actual C. Hoffman *et al.*, Endocrinology Vol. 134 (1): pp. 264-270 reference was cited in an IDS and form PTO-1449 by Applicants as reference A9.

The comment by Stevenson *et al.* is mere conjecture at best, and does not attempt to assert a method of treatement. Hoffman *et al.* do not teach a method for treating TNF-α mediated

complications of diabetes by the administration of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (pioglitazone).

The cited conjecture by Stevenson *et al.* should not be substituted for the actual teaching of the primary reference. Stevenson *et al.* even admits that the primary reference, in fact teaches that the described effect on TNF-α cannot be attributed to administration of pioglitazone alone. Thus, the statement cannot be construed as teaching a method for treating Tumor Necrosis Factor-alpha (TNF-α) mediated diabetic complications. The mere suggestion that TNF-α is associated with diabetes does not teach the specifically claimed method for treating TNF-α mediated diabetic complications with pioglitazone and/or rosiglitazone of the present invention.

A new method of treatment for a previously know chemical compound is not anticipated by the administration of the compound in a previously known method. In the invention of Claim 1 as amended, is specifically for the administration of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (pioglitazone) for the treatment of Tumor Necrosis Factor-alpha (TNF-α) mediated diabetic complications. This is distinct from the treatment of diabetes as was taught in the art.

The Examiner admits that none of the asserted art teach treatment of TNF-alpha mediated inflammation. (Paper 13, Page 7, 1st paragraph, and Page 9, 4th paragraph). There is no evidence on record to support maintaining this rejection. The Examiner has admitted that "the prior art does not expressly disclose the employment of the particular thiazolidinedione derivative, 5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, in a method for treating a Tumor Necrosis Factor-α mediated diabetic complications in a mammal, and its effective amount." (Paper 15, page 4, 3rd paragraph).

The causes of diabetes, and the related pathologies are complex. It is improper to mistakenly over-characterize the teaching of the art, and then to assert that the general teachings of treatment of diabetes can be used to suggest the presently claimed invention as obvious. There is no evidence of record that demonstrates that one of ordinary skill in the art would have been motivated to treat TNF-α mediated inflammation in diabetic patients.

The Examiner's rejection is tainted by hindsight use of the presently claimed invention to selectively interpret the cited art, improperly, so as to support the Examiner's pre-determined conclusions.

This rejection should be withdrawn.

V. Conclusion

Reconsideration and allowance of the claims as amended is requested.

Should the Examiner believe that a conference with Applicants' attorney would advance prosecution of this application, the Examiner is respectfully requested to call Applicants' attorney at the number below.

Respectfully submitted,

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